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PATENT

Customer Number 22,852

Attorney Docket No. 1147-0142

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of: U.S. Patent No. 5,750,338	)	
Mark L. Collins et al.	)	Group Art Unit: 1655
Reissue Serial No.: 09/533,906	)	Examiner: D. Johannsen
Reissue Application Filed: March 8, 2000	)	
For: TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS	)	

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Assistant Commissioner for Patents

Washington, D.C. 20231

Sir:

PATENT OWNER'S RESPONSE TO GEN-PROBE'S PROTEST

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In response to the Communication Regarding Protest, issued by the Office on October 25, 2000, the Patent Owner submits the following remarks.[1]

I. Introduction

A. The Claimed Invention and Its Significance

The invention claimed in U.S. Patent No. 5,750,338 (the '338 patent) and in this application to reissue the '338 patent has proven to be highly significant in the development of sensitive, automated, nucleic-acid-based detection systems of the sort required, for example, to screen the nation's blood supply for dangerous viral pathogens such as HIV and Hepatitis C. While the development of the so-called "polymerase chain reaction" (PCR) and other such *in vitro* techniques for the amplification of polynucleotides was originally believed to provide the ability to detect target polynucleotides present in very small amounts in complex samples, this has not proven to be the case. The presence of non-target polynucleotides in the sample that are amplified along with the target has proven troublesome, as has the presence in the sample of inhibitors and other substances that interfere with the amplification process. So troublesome has this aspect of such assay systems become that it has been called the "Achilles' heel" of nucleic acid amplification tests.

The present invention overcomes this "Achilles' heel" by providing for the capture of the target polynucleotide, whereby the target is separated from non-target polynucleotides and other interfering substances in the sample, prior to being subjected to one of the several available *in vitro* amplification and detection processes. This combination of steps was demonstrated to be

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1 The due date for the comments, originally set for November 25, 2000, was extended at the request of Patent Owner's representative, to January 15, 2001.

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nonobvious during procurement of the original '338 patent because, *inter alia*, the prior art relating to PCR taught away from the invention by suggesting that initial separation steps were unnecessary. Indeed, such additional sample handling steps, which add mechanical complexity to automated systems and carry with them the omnipresent threat of loss of target polynucleotides present in only very small amounts, would have been contraindicated in the development of highly automated and sensitive systems of the sort in which the present invention has found its most immediate application.

The importance of the present invention is attested to by the actions of those who have appropriated it and who are now trying to destroy the patent. Gen-Probe Incorporated (Gen-Probe), a wholly owned subsidiary of a multinational Japanese drug company, Chugai Pharmaceuticals Inc. (Chugai), has incorporated the present invention into a highly automated, sensitive, nucleic-acid-based system for the detection of HIV and Hepatitis C in the nation's blood supply. Gen-Probe is doing so in the context of an alliance with Chiron Corp. While Gen-Probe has filed a declaratory judgment action in the U.S. District Court for the Southern District of California seeking to invalidate the '338 patent, and has filed a protest against the grant of this reissue application, the depth of Gen-Probe's conviction in the merit of its current contentions must be judged in light of the fact that it has done so only after it secured a license under the '338 patent. To this day, Gen-Probe has not canceled or otherwise repudiated that license and, in fact, continues to pay royalties under the license. Gen-Probe and Chiron certainly believe that this blood screening system embodying the present invention will be a huge commercial success,

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resulting in the payment of large royalties for use of the licensed invention.[2] Moreover, both contemplate introduction of additional new products utilizing the invention (Ex. 25). While this surely provides an economic motive to try to invalidate the patent, the underlying facts clearly demonstrate the nonobviousness and patentability of the invention rather than the opposite. This is undoubtedly why Gen-Probe pursues its present course only under the protective umbrella of its extant license under the '338 patent.

Gen-Probe's conduct in developing its blood screening detection system highlights the nonobviousness of the present invention. Just as the Patent Owner had contended with respect to the prior art in prosecution of the '338 patent, Gen-Probe came very late to the realization that an additional step of target capture was desirable prior to *in vitro* amplification in nucleic-acid-based detection systems. Indeed, Gen-Probe's own patent filings reflect the bias in the art against the inclusion of additional steps in such assays. For example, Gen-Probe's U.S. Patent No. 5,639,599 (Ex. 3) provides for the addition of the cell lysate directly to the amplification reaction without further purification to "minimize the complexity and manipulations involved in practical, routine use of target amplification." Col. 11, lines 39-44.

Gen-Probe does not appear to have recognized the value and importance of target capture prior to *in vitro* amplification until 1996-97 -- after it had hired scientists familiar with the technique from their work at Gene-Trak Systems[3], the predecessor of the present assignee of the

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2 Market analysts have estimated the market potential for these products as $400-500 million per year, have estimated sales of the products of $31.9 million in the year 2000 (even though the test has yet to be formally approved in the U.S.), and projected sales of $275 million by the year 2005 (Exs. 24 and 25).

3 The name Gene-Trak Systems or Gene-Trak refers to a succession of business entities (continued...)

'338 patent. Since its belated recognition of the importance of this technique, Gen-Probe has embraced target capture as a method of processing samples. Indeed, Gen-Probe has described sample processing as "the Achilles' heel" of nucleic acid amplification tests, characterized the concept of "target capture" on its web site as "new," and claimed that this new target capture technology addresses the "Achilles' heel" of such assays.

Having come so late to appreciate the importance of initial target capture to its nucleic acid amplification assays, Gen-Probe nonetheless attacks the patentability of the contribution made by the present inventors who did have such an appreciation many years earlier in 1987. Gen-Probe does so by urging the PTO to adopt an interpretation of the term "amplifying" in the pending claims that is a gross departure from anything described in the '338 patent, reflected in the prosecution history of the original '338 patent, or rationally contemplated by the inventors, the examiner, or anyone seeking to practice the claimed invention.

Specifically, Gen-Probe suggests that the term "amplifying" should be construed so broadly as to encompass *in vivo* cloning operations and the like, even though no such techniques are described or contemplated anywhere in the text of the '338 patent. By straining the intended meaning of the claim language beyond the pale of reasonableness, Gen-Probe alleges anticipation of the original patent claims by a diverse spectrum of prior art that has nothing whatsoever to do with nucleic-acid-amplification-based detection assays.

Sensing the inadequacy of this position, Gen-Probe further alleges obviousness based on grossly speculative musings about the future of molecular biology in a 1974 review article which,

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[3](...continued)
which preceded, but are now owned by, Patent Owner.

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if given the weight Gen-Probe urges, would have invalidated the fundamental PCR patent itself, which it clearly did not. That Gen-Probe itself and others in the art did not recognize the need for and desirability of the claimed invention until after the present inventors had done so in 1987 belies Gen-Probe's contention that the 1974 vintage literature placed the invention in the public domain.

B. The Prosecution History of the '338 Patent

The substantive prosecution of the '338 patent began with the Office Action issued in the prior related application, U.S. Serial No. 07/944,505,[4] which the Patent Owner submitted to facilitate prosecution. *See* Preliminary Amendment of December 5, 1995. That Office Action rejected all pending claims as unpatentable over Mullis, a primary reference that disclosed "DNA amplification." The Examiner explicitly recognized that the primary reference did "not specifically teach nucleic acid affinity chromatography prior to the amplification reaction" and, accordingly, relied on several secondary references that taught "the well known method of affinity chromatography." The Mullis reference, U.S. Patent No. 4,683,202 (Ex. 1), is, of course, the well known PCR patent. Because neither the primary nor the secondary references suggested the combination of the two techniques of target capture and amplification, the examiner essentially relied on the desire to improve sensitivity as allegedly establishing a motivation to combine their teachings.

In response, the Patent Owner pointed out that the Mullis patent actually taught away from the claimed combination of purification prior to amplification, quoting from Mullis that

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[4] The same rejections and the same art had been raised in the Office Actions in the earlier related cases. *See* USSN 07/136,920, Office Action of July 20, 1990; and USSN 07/644,967, Office Action of March 12, 1992.

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"the present invention obviates the need for extensive purification of the product from a complicated biological mixture" (col. 2, lines 32-34), and that:

> It is not necessary that the sequence to be amplified be present initially in a pure form; it may be a minor fraction of a complex mixture... or a portion of nucleic acid sequence due to a particular microorganism which organism might constitute only a very minor fraction of a particular biological sample.

Col. 5, lines 49-56. *See* Preliminary Amendment of December 5, 1995, at page 16. In addition, to the extent that the Mullis patent considered any need for removal of non-target sequences to reduce non-specific amplification, it suggested a very different solution, the use of nested primers (Ex. 10, at col. 25, line 23 to col. 26, line 29). *Id.* As to the secondary references, the Patent Owner reiterated that none disclosed or suggested amplification.

The Patent Owner also cited a number of later references (Schochetman, Vosberg, PCR Protocols, Coutlee, and Miller) that demonstrate that practitioners of PCR eventually did recognize that PCR did not obviate the need for purification of a product. Nonetheless, despite the recognition of the need for purification, none of these references suggested the claimed solution of target capture prior to amplification. Preliminary Amendment of December 5, 1995, at pages 17-19.

The examiner did not maintain the rejection based on Mullis in the next Office Action. Office Action of June 20, 1996. Instead, the Examiner asserted another rejection under Section 103, based on a patent to Vary (U.S. Patent No. 4,851,331), which taught amplifying a target and then immobilizing the amplified target on a support for separation and detection. The examiner did recognize that this reference did not teach the binding of a "target polynucleotide to a support or [to] separate the target from the sample prior to amplification." *See* Office Action at page 4.

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In an effort to find the elements of the claimed invention in the prior art, the examiner then relied on a secondary reference (Henson) that taught hybridization of a sequence of interest to a probe which could be immobilized. The examiner urged that "enriching for a desired target sequence in a population of sequences prior to a PCR amplification step would provide a more sensitive assay." *Id.* at page 5.

In response, the Patent Owner again pointed out the teaching away in Mullis and the failure of subsequent PCR practitioners to suggest the claimed invention even after recognizing the need for it. Amendment of October 24, 1996, at pages 10-13. Nonetheless, the examiner maintained the rejection. Office Action of January 7, 1997, at pages 5-7.

To address the maintained rejection, the Patent Owner introduced a reference that described the claimed combination of target purification prior to amplification, termed "Sequence Capture-PCR," as a "new" procedure in 1996.[11] As an indication of the art's recognition of the value of the combination, the Patent Owner also submitted a contemporaneous review article that characterized the new procedure as a "significant advance."[12]

The Patent Owner also submitted the declaration of Dr. David Persing to address the examiner's belief that those in the art would have been motivated to employ target capture prior to amplification. Dr. Persing is the Editor-in-Chief of the text book DIAGNOSTIC MOLECULAR

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[11] Gilles Mangiapan et al., *Sequence Capture-PCR Improves Detection of Mycobacterial DNA in Clinical Specimens*, J. Clin. Microbiol., 34:1209-1215 (1996) (Ex. 8).

[12] Margareta Ieven and Herman Goossens, *Relevance of Nucleic Acid Amplification Techniques for Diagnosis of Respiratory Tract Infections in the Clinical Laboratory*, Clin. Microbiol. Rev., 10(2):242-256 (1997), at page 248, right column, first paragraph (Ex 9).

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MICROBIOLOGY and is a recognized expert in the field of the techniques of amplification and hybridization, particularly in the area of infectious diseases.

According to Dr. Persing, the examiner's belief that it would have been obvious to employ target capture prior to amplification "overlooks or greatly oversimplifies the problems actually encountered by practitioners attempting to obtain highly sensitive assays using target amplification." Persing Declaration, ¶ 12. First, the addition of extra steps to hybridization assays added "an additional, significant level of complexity" to the assay which skilled persons would avoid absent some clear benefit.[13] In addition, viewing it from the standpoint of practitioners of amplification, those in the art believed that PCR was so highly specific, based as it was on the careful selection of primers, that there was no need to isolate or separate target polynucleotides. *Id.* And, according to Dr. Persing, it was not until after December 1987 that those in the art recognized that careful selection of primers was not enough to avoid problems such as non-specific amplification. *Id.*

From the binding and separating standpoint, it was generally understood that binding of the target to a probe on a support was "substantially less than 100%." Thus, for assays in which the level of target polynucleotide was low, the use of a binding and separating step would decrease the already low amount of target available for detection. Persing Declaration, ¶ 13. Accordingly, Dr. Persing concluded that:

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[13] Although not noted at the time in prosecution, patents in the field, including Gen-Probe's own patents, bear out this reluctance to add complex steps. For example, Gen-Probe's U.S. Patent No. 5,639,599 (Ex. 3) suggests a step of adding the cell lysate directly to the amplification reaction without further purification to "minimize the complexity and manipulations involved in practical, routine use of target amplification." Col. 11, lines 39-44.

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[C]oupled with the conventional understanding at that time (that careful selection of primers would permit adequate selectivity of target and specificity in the amplification product), the practitioners' concern regarding imperfect binding efficiencies and the expected loss of real target before amplification occurred reinforced their incentive to avoid further complicating their assays by the addition of target separation steps to their assays.

Persing Declaration, ¶ 13.

Dr. Persing also noted an advantage of the claimed method that was not generally appreciated, specifically, that separating the target prior to amplification eliminates the effect of amplification inhibitors that are normally present in the sample system. This removal of inhibitors permits amplification to proceed optimally. Persing Declaration, ¶ 14.

The examiner agreed, stating in the Notice of Allowance that:

[T]he art at the time of filing did not recognize that the efficiency of PCR amplification would decrease due to the presence of contaminants in a sample and therefore provided no motivation to purify a target sample from a heterogenous sample of nucleic acids prior to amplification. Having not recognized the problem, applicant's solution therefore, while utilizing routine methodology to modify PCR amplification techniques, would not have been obvious at the time that the invention was made. The Declaration of Dr. David Pershing[sic] [ ] further supports this conclusion as providing further evidence concerning the skill of the art at the time of filing, attesting that one of skill in the art would likely stay away from combining a hybridization capture method with a PCR method since one would not be motivated to provide a method with the potential to lose target nucleic acids prior to amplification.[14]

Thus, claims 1-40 issued. The claims recite methods of amplification (independent claims 1, 27, and 34), methods of detection (independent claims 7, 19, 28, and 38), and kits

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[14] While the claims are properly limited to *in vitro* amplification methods that produce a multitude of polynucleotide amplification products like PCR, they are not strictly limited to PCR. See §II, below. This is clear from the inclusion of dependent claims that involve enzymes that were not and are not used in classic PCR (RNA polymerase and Qβ replicase (claims 5 and 11)). See also Preliminary Amendment of December 5, 1995 at page 12, noting that the targets can be amplified with "a variety of methods."

(independent claims 20 and 24). The claims provide for a variety of methods for separating the target polynucleotide, the simplest being providing a support to which the target polynucleotide binds and then removing the support from the sample (claims 1 and 7). Alternatively, the claims specify separation of the target by providing a probe which binds to the target and then providing a support which binds to the probe (claims 27 and 28) or by providing a support and a probe that binds to the target and to the support (claim 34 and 38). Similarly, the claims provide for a variety of methods for amplifying the separated target polynucleotide. The target polynucleotide can be amplified with a polymerase (claims 4, 10, 17, 25, 29, 35 and 39), or a DNA polymerase, an RNA polymerase, a transcriptase, or Qβ replicase (claims 5, 11, 30, and 36).

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C. The New Reissue Claims

In the Preliminary Amendment that accompanied the reissue application, the Patent Owner added claims 41-59.[15] New claims 41, 47, and 53-59 make explicit several aspects that were implicit in the amplification steps originally claimed. Specifically they recite *"in vitro"* amplification[16] which produces a "multitude"[17] of "polynucleotide amplification products."[18]

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[15] To facilitate the review of the newly added claims, the following table identifies the type of claim and the original claim from which the newly added claims depend.

Type of claim	Original claim	Added claim
Method of amplification	1	41-46
	27	56
	34	58
Method of detection	7	47-52
	19	53
	28	57
	38	59
Kits	20	54
	24	55

[16] As support in the '338 patent for *in vitro* amplification, the Patent Owner notes that:

- Example 4 describes amplification via *E. coli* RNA polymerase that lacks the sigma subunit (i.e., core RNA polymerase) together with nucleotide triphosphates and a low salt transcription buffer. See col. 30, line 59 to col. 31, line 19.

- Example 5 sets forth a two stage process of amplification, first using DNA polymerase, random oligohexamer primers, and deoxynucleotide triphosphates in buffer to replicate the DNA and to produce additional double stranded DNA, followed by the addition of core RNA polymerase, nucleotide triphosphates, and a low salt transcription buffer to form many RNA copies of the DNA. See col. 31, lines, 28-54.

(continued...)

In addition to these claims, the Patent Owner added claims to specify additional aspects of the amplification method. Thus, claims 42, 45, 48, and 51 claim amplification wherein the amplification is "linear or exponential."[19] Further dependent claims 43 and 49 specify an exponential amplification process. The Patent Owner has also added dependent claims 44 and 50 to recite the use of a polymerase and at least one oligonucleotide primer because the specification

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[16](...continued)
- Example 6 amplifies first by non-specific double stranded DNA synthesis, as set forth in the first part of Example 5, followed by cycles of heating to form single stranded DNA and then polymerizing with additional DNA polymerase to yield an approximately 1,000 fold increase in the level of DNA. See col. 31, line 60 to col. 32, line 5.

- Example 7 describes the exponential replication of RNA with Qβ replicase. See col. 32, lines 10-19.

[17] Express literal support in the '338 patent for this element is set forth in the specification, which states that "In Step 3 of FIGS. 4, 5, and 6, the isolated target is non-specifically amplified to form a multitude of amplification products." See col. 15, lines 56-58. In addition, because each of Figures 4, 5, and 6 corresponds to Examples 4, 5, and 6, respectively, these examples also support this limitation.

[18] This limitation finds support in the '338 patent in the definition of amplification, which recites enzymes that can only produce polynucleotide amplification products from polynucleotide targets, as follows:

> In the situation where the target is a polynucleotide, additional target, or target-like molecules, or molecules subject to detecting can be made enzymatically with DNA or RNA polymerases or transcriptases.

See col. 2, lines 16-19. In addition, all of the amplification examples (Examples 4-7) result in the production of polynucleotide amplification products, i.e., either RNA or DNA.

[19] For support, Examples 4 and 5, with their one-at-a-time transcription of RNA and/or replication of DNA, are linear, while Examples 6 and 7, with the doubling of DNA per cycle, provide for exponential replication. Indeed, Example 7 expressly notes the exponential nature of the process at col. 32, lines 17-19.

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covers amplification both with and without primers.[20] In addition, claims 46 and 52 cover amplification methods based on more than one polymerase."[21]

II. Claim Construction

Before addressing the specifics of Gen-Probe's Protest, it is useful to address the construction of the term that appears again and again in the Protest, specifically, the term "amplifying." Claim construction is the necessary "first step" in any validity analysis. *See Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1362, 44 U.S.P.Q.2d 1027, 1029 (Fed. Cir. 1998).

The three primary tools for interpreting claims are the claims, the specification, and the prosecution history. *Markman v. West-view Instruments, Inc.*, 52 F.3d 967, 979, 34 U.S.P.Q.2d 1321, 1329 (Fed. Cir. 1995) (in banc), *aff'd*, 517 U.S. 370, 116 S. Ct. 1384 (1996). The language of the claims themselves is always the appropriate starting point for any claim construction. *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 619, 34 U.S.P.Q.2d 1816, 1819 (Fed. Cir. 1995).

Claims, however, must be read in view of the written description in the patent specification of which they are a part. Thus, the written description may act as a sort of dictionary that explains the invention and may define the terms used in the claims. *Markman,* 52 F.3d at 979, 34 U.S.P.Q.2d at 1330.

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[20] The support for claims with primers is expressly set forth in Examples 5-6, while the support for amplification without primers is set forth in Example 4.

[21] Example 5 sets forth the support for this aspect of the invention.

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The patent's prosecution history must also be considered in construing claim language. *Markman,* 52 F.3d at 980, 34 U.S.P.Q.2d at 1330. There is no doubt that this "undisputed public record" of proceedings in the PTO is of primary significance in understanding the claims. *Id.*

The term " amplifying" first appears in claim 1 of the '338 patent, which recites:

> 1. A method for amplifying a target polynucleotide contained in a sample comprising the steps of:
>
> (a) contacting the sample with a first support which binds to the target polynucleotide;
>
> (b) substantially separating the support and bound target polynucleotide from the sample; and
>
> (c) amplifying the target polynucleotide.

The same term "amplifying" also appears in claim 7 directed to a method of "detecting a polynucleotide contained in a sample" and claim 20 directed to a "kit for detecting a target polynucleotide contained in a sample." Because there is no indication of any intention that the term should have different meanings in these different claims, the text of the claims themselves indicates that the term "amplifying" must connote amplifying in a manner logically appropriate for use in a detection method and kit. Contrary to Gen-Probe's assertions, *in vivo* cloning is not an amplification technique generally useable in detection kits. Indeed, at least one Gen-Probe patent on amplification specifically recognizes that cloning is not even appropriate in diagnostic testing, stating:

> Although cloning allows the production of virtually unlimited amounts of specific nucleic acid sequences, due to the number of manipulations involved it may not be suitable for

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> use in diagnostic, environmental, or forensic testing. Use of cloning techniques requires considerable training and expertise. The cloning of a single sequence may consume several man-months of effort or more.

U.S. Patent No. 5,399,491, col. 3, lines 42-49 (Ex. 2).

While the text of the patent contains a general definition of amplification (col. 2, lines 9-19), that definition does not indicate that the term includes *in vivo* methods. Indeed, the description of the actual steps of amplification in the remainder of the specification leaves no doubt that it is an *in vitro* enzymatic step that produces multiple copies of polynucleotide amplification products.[23]

For example, the '338 patent specification describes several embodiments of amplification based on RNA polymerase, Qβ replicase, reverse transcriptase, and DNA polymerase at column 15, line 39 to column 16, line 29. Each of these embodiments is an *in vitro* amplification process. Similarly, Examples 4-7 describe only *in vitro* methods of amplification, with Examples 4, 5, and 6 corresponding to Figure 4, 5, and 6, respectively. Example 7 further describes the exponential replication of RNA *in vitro* with Qβ replicase.

More importantly, the prosecution history demonstrates that the examiners understood the claims to be directed to *in vitro* methods of amplification. The only amplification art cited against the claims disclosed *in vitro* amplification, including the basic PCR patent. This is true despite the existence of, as Gen-Probe noted, "processes such as cloning, cell-free translation and synthesis of cDNA from mRNA, all of which were basic techniques of molecular biology in

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[23] While the foregoing discussion has focused on cloning, precisely the same analysis is applicable with respect to the other alleged "amplification" techniques in the prior art cited by Gen-Probe. Cell free translation, Sanger sequencing, and the like are not the types of *in vitro* amplification techniques that are appropriate for use in detection kits and are wholly unlike the techniques illustrated in the specification of the '338 patent.

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December 1987." *See* Protest at page 4. Indeed, the examiner that allowed the application was so certain of the limitation of the claims to *in vitro* enzymatic methods that she focused on the nonobviousness of using the invention in the context of *in vitro* amplification methods, specifically PCR, in stating the reasons for allowing the claims.

Finally, the Patent Owner wishes to interject a note of reality. Every person skilled in this art recognizes the significant and fundamental difference between cloning and *in vitro* amplification. The PCR patent (Mullis '202) itself notes at the outset the difference between molecular cloning and the enzymatic-based amplification of its invention. According to Mullis, PCR "does not involve the propagation of any organism and thereby avoids the possible hazards or inconvenience which this entails." Col. 2, lines 26-30 (Ex. 1). It cannot rationally be suggested that either the technically trained inventors or the technically trained examiners of the original '338 patent could possibly have interpreted the term "amplifying" in the '338 patent to encompass *in vivo* cloning, as Gen-Probe now suggests. Had the term been so interpreted, some of the earliest experiments in the field of recombinant DNA would have been pertinent prior art, such as the cloning of mammalian genes (the rabbit globin gene and the rat insulin gene) that proceeded by the preparative isolation of mRNA on an oligo-dT (or oligo-dU) column followed by cloning.[24] That the entire original prosecution of the '338 patent proceeded without reference to these landmark experiments makes clear that neither the inventors nor the examiner ever interpreted the word "amplifying" as broadly as Gen-Probe now argues.

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[24] Axel Ullrich et al., *Rat Insulin Genes: Construction of Plasmids Containing the Coding Sequences*, Science, 196:1313-1319 (1977) (Ex. 10); Russ Higuchi et al., *A General Method For Cloning Eukaryotic Structural Gene Sequences*, Proc. Natl. Acad. Sci. USA, 73:3146-3150 (1976) (Ex. 11).

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Accordingly, when the term "amplifying" is properly construed as referring to techniques suitable for use in detection processes and kits of the sort to which the specification is entirely restricted, there is no doubt that it connotes an *in vitro* enzymatic process that produces a multitude of copies of polynucleotide amplification products.

III. The Claims Are Not Anticipated by Gen-Probe's Cited Art

None of the four references cited by Gen-Probe anticipates any of the claims of the '338 patent in issue.[25]

A. Arsenyan et al. Does Not Disclose Amplification, Detection Methods, or Kits

Arsenyan, a 1980 report on the isolation of rat liver 5S genes, isolated the gene by "(a) enrichment of DNA fragments carrying the genes of interest, and (b) subsequent cloning and amplification of these fragments." The amplification was via cloning into the *Eco*RI site of pBR322, using *E. coli* as a host.

Among the deficiencies of Arsenyan as an allegedly anticipatory reference, the most significant may be its failure to teach amplification within the meaning of the claims. Gen-Probe argues throughout the first 30 pages of its Protest that amplification was defined so broadly in the specification that it encompasses any process by which copies of target polynucleotides could be produced (*see, e.g.*, Protest at page 4), and specifically urges that Arsenyan's disclosure of growing transformed *E. coli* was within the claim element "amplifying" (*see* Protest at page 21-

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[25] Gen-Probe suggests, at footnote 8 on page 21, that there is more anticipatory prior art because the '338 patent is not entitled to its priority date. The allegation is not further developed by Gen-Probe for good reason. The priority issue raised by the PTO to which Gen-Probe refers was raised in a different application that is a CIP of the '338 patent. Moreover, that issue was resolved favorably to the Patent Owner. In fact, the Notice of Allowance in that case contained an Examiner's Amendment that amended the application to recite the Patent Owner's claim to priority back to the first case, filed October 23, 1986.

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22). However, Gen-Probe makes this assertion without first construing the claim and the term "amplifying." As noted above, when properly construed, the term "amplifying" refers to *in vitro* enzymatic methods of producing a multitude of polynucleotide amplification products. Even if Gen-Probe's strained reading of the word "amplifying," a reading divorced from the text and prosecution history of the '338 patent, were relevant to construction of the original claims of the '338 patent (which it is not), Arsenyan clearly fails to anticipate the new reissue claims that explicitly require *in vitro* amplification. Nor does the reference describe or suggest the detection methods or kits specified by many of the pending claims.

B. Boss et al. Does Not Disclose Amplification, Detection Methods, or Kits

According to Gen-Probe, Boss discloses the isolation of yeast mRNA by hybridization and subsequent "amplification" by "enzymatically producing the isolated sequence in a dideoxy chain termination reaction." This reaction, more commonly known as the "Sanger" reaction, is a method of sequencing, not an amplification method. As indicated by the title of the method, it creates polynucleotide fragments of different lengths, each ending with a labeled and chain-terminating nucleotide. Thus, it is simply not a method of amplifying a particular target polynucleotide. Nor does the reference describe the detection methods or kits specified by many of the pending claims.

C. Gaubatz et al. Does Not Disclose Either Amplifying or Detecting a Target Polynucleotide

According to Gen-Probe, Gaubatz purified globin mRNA by chromatography which was then "amplified" based on its hairpin loop structure using the "displacement synthesis" method. In the first instance, the objective of Gaubatz is to prepare cDNA for *in vivo* cloning (p. 186, col.

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1, 2nd paragraph) -- a form of "amplification" unsuited for nucleic acid detection assays and not within the scope of the term "amplifying" used in the claims for reasons noted above. There is certainly no disclosure of use of this technique to detect nucleic acid targets in samples or kits for that purpose.

To the extent that an intermediate step is undertaken in an effort to increase the concentration of the coding sequences derived from the mRNA, so-called "displacement synthesis," the reference is equivocal as to whether amplification actually took place at all and explicitly indicates that the result of the "displacement synthesis" was not a faithful reproduction of the target messenger RNA.

Specifically, the authors note (pg. 185, col. 2 to pg. 186, col. 1):

> Although a fraction of the displacement product is globin cDNA, it has not been shown that the entire increase in cDNA mass is due to a corresponding increase in globin sequence. *** Furthermore, the results indicate that amplified cDNA exists in a large multistrand complex which contains some single-stranded material; under denaturing conditions, however, displaced cDNA and replication intermediates can be resolved into size classes corresponding to full-length globin cDNA. The nature of the intermolecular associations between displaced strands and replication intermediates is not known. Further studies using electron microscopy and other techniques might elucidate the structural features of these complexes.

The authors note further that the method is capable of producing "an inverted symmetrical arrangement of two cDNA segments each containing approximately half of the 3' mRNA sequences [with a] 5' region of mRNA sequences and a small oligo (d G · d C) sequence separat[ing] the inverted repeats." Page 186, col. 1. Moreover, the method is acknowledged to produce "reaction products greater than full-length globin cDNA" (page 186, col. 2) as well as "shorter cDNA containing single-stranded regions" (page 181, col. 2). Whatever may have been

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the merit of the proposed displacement synthesis scheme for increasing the likelihood of cloning pieces of DNA having some coding sequences somewhere in them, the proposed approach was not a method of faithfully amplifying target DNA suitable for use in a nucleic acid detection assay and does not anticipate any of the pending claims. Further, the myriad processing steps included in the Gaubatz process (numerous organic extractions, chromatographic separations, ethanol precipitations, and polysomal preparations) render it plainly unsuitable for use in a diagnostic kit, instrumented assay, or other detection assay.

D. Powell et al. Does Not Anticipate the Pending Claims

Powell is also not directed to any technique suitable for use in nucleic acid detection assays on clinical samples or in kits. No such detection assays or kits are described. Indeed, the techniques described by Powell, which would take at least several days to complete, are wholly unsuitable for nucleic acid detection assays on clinical samples. The microgram quantities of mRNA used in the techniques (page 839, col. 1, paragraph 5) also highlight the unsuitability of the disclosed techniques in detection assays -- assays where the acknowledged challenge is developing systems that are sensitive enough to detect the very minute amounts of target nucleic acid material available in the usual clinical sample.[26]

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[26] In U.S. Patent No. 5,399,491 (Ex. 2), Gen-Probe itself states:

> The most sensitive procedures may lack many of the features required for routine clinical and environmental testing such as speed, convenience, and economy. Furthermore, their sensitivities may not be sufficient for many desired applications. Infectious diseases may be associated with as few as one pathogenic microorganism per 10 ml of blood or other specimen. Forensic investigators may have available only trace amounts of tissue available from a crime scene. Researchers may need to detect and/or quantitate a specific gene sequence that is present as only a tiny fraction of all the sequences present in an organism's genetic material or in the messenger RNA population of a group of cells.

(continued...)

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Beyond the foregoing, Powell does not perform a target capture step for the purpose of enhancing the efficiency of a subsequent *in vitro* amplification step. Powell instead describes the use, in some but not all cases, of the trivial step of separating by absorption on an oligo-dT column all the cellular mRNA molecules (which have poly A tails) from associated ribosomal RNA molecules (which do not have poly A tails), which had already been separated from the cellular milieu by other means. Indeed, Powell actually teaches away from the need to employ such a separation step prior to amplification in that a number of the PCR amplifications described in the legend to Figure 5 were done with total RNA, not poly A + RNA. This confirms that separation of messenger RNA from total RNA on an oligo-dT column was neither necessary to nor important for the PCR amplification conducted by Powell.

IV. Both the Originally Filed Claims and the Claims Added in Reissue Are Nonobvious Under 35 U.S.C. § 103

A. Introduction

Despite the size of Gen-Probe's Protest, its primary argument hinges on a single speculative sentence in the "Concluding Remarks" of a 1974 review of techniques for isolating genes, which states:

> Clearly, purification of important structural genes will have to be coupled with some method in which a small amount of a given gene can be increased enormously in amount.

Donald D. Brown and Ralph Stern, *Methods of Gene Isolation*, Ann. Rev. Biochem., 43:667-693 (1974) at page 687. As discussed below, however, neither the Brown reference nor any other reference cited by Gen-Probe renders the claimed invention unpatentable under 35 U.S.C. § 103.

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[26](...continued)
Col. 2, lines 9-21.

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Not only does Brown's speculation fail to suggest the invention of the reissue application, Gen-Probe's own documents belie the belatedly alleged obviousness of the claimed invention. The claimed combination of target capture prior to amplification apparently did not occur to Gen-Probe until the mid-1990's, where it is expressly disclosed in a Gen-Probe patent that was applied for in July 1997 (Ex. 7). Though here alleged to have been obvious, the combination of target capture and amplification is touted as "new" and one of Gen-Probe's five "Core Technologies." A quick visit to Gen-Probe's website (Ex. 26), reproduced in part below, demonstrates the significance of target capture before amplification:

> **Target Capture**
>
> **Purification of Target Molecule before Amplification**
>
> The major limitation of current nucleic acid amplification assays is the sample processing step which is usually complex, time-consuming, and often does not eliminate interfering substances that can inhibit the amplification reaction. Target Capture is a **new** sample-preparation technology, which partially purifies the target nucleic acid before the amplification process. [Emphasis added.]

Consistent with Gen-Probe's late recognition of the value of target capture before amplification, the early literature taught that nucleic acid amplification based on primers did not require a prior purification step. Accordingly, despite the existence of both nucleic acid hybridization and amplification techniques prior to the invention, the need for and desirability of nucleic acid target purification prior to *in vitro* amplification in the context of nucleic acid detection assays was not obvious -- just as Dr. Persing attested during the prosecution of the '338 patent now in reissue. See § I.B, above.

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B. The Speculative Statements in the 1974 Brown Review

With the benefit of hindsight, and in an effort to reconstruct from the prior art a motivation to do what the present inventors have done, Gen-Probe relies on a review published in 1974, a full thirteen years before the present inventors or anyone else (and apparently over 20 years before Gen-Probe itself) recognized the benefit of target capture prior to amplification in nucleic acid detection assays. The review, entitled *Methods of Gene Isolation*, describes the techniques of gene isolation then available, but this early piece begins and concludes the discussion of then current methods with prophetic statements on the potential value of isolated genes. For example, the Introduction speculates that:

> It **should** be possible to study the initiation, termination, and promoter regions of specific genes. * * * The control mechanisms in eukaryotes **might** be unraveled by their reconstruction *in vitro*, just as has been done in bacteria. A purified gene **would** be mixed with the proper molecules, and exact initiation and termination by the correct RNA polymerase **should** take place. With such an assay, it **may** be possible to understand control of gene action in eukaryotes. Gene isolation and characterization **may** well play a prominent role in the understanding of chromosome structure and chromosome pairing, and in the analysis of meiotic and mitotic recombination [Emphasis added.]

After 10 pages of techniques that do not disclose or suggest the invention, the concluding section reverts to speculation and describes what might be possible with the isolated genes. To most completely convey the obviously speculative flavor of the expressed hopes of the authors for the use of genes, we quote extensively from the conclusion, with some of the more blatant conjecture in bold:

> Isolation of a gene as native DNA permits any experiment that can be carried out with the purified coding strand plus a variety of others. * * * The present methods for native DNA isolation are applicable to reiterated genes such as rDNA, 5SDNA, and the genes for transfer RNA .... **It is likely that these DNA components can be isolated from a wide variety of animal DNAs by one of**

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the methods for native DNA fractionation described here. The histone genes appear to be present in multiple copies in some genomes, and these genes should be easy to purify. However, evidence is accumulating which shows that there will be few, perhaps only one, structural genes per haploid genome in eukaryotes. * * * One gram of starting DNA would contain 0.17 μg of this [the globin] gene. This formidable purification problem is compounded by the presence of neighboring sequences of unknown composition on either side of single genes which will vary considerably.... **For this reason, a restriction enzyme will have to be found which specifically cleaves the DNA into homogeneous fragments,** preferably pieces containing the structural gene and some sequences on either side.

Clearly, **purification of important structural genes will have to be coupled with some method in which a small amount of a given gene can be increased enormously in amount. After purification has enriched the gene sequence about a thousandfold the remaining DNA would be amplified hundreds- to thousandsfold in amount. Purification could then be continued. The amplification step might be carried out in vitro by an efficient DNA polymerase,** which would replicate faithfully each molecule of DNA many times. Alternatively, insertion of the DNA into a phage or bacterial episome, followed by infection and growth within a bacteria, **could** produce large amounts of homogeneous DNA components. **This last method has the advantage of cloning individual DNA molecules from an impure mixture of DNA.**

Given a pure RNA product of any gene, it should be possible to isolate a coding strand. * * * The larger the DNA fragments, the more the RNA-DNA hybrid will behave like ssDNA and the less successful will be the fractionation. These problems limit the technique to ssDNA molecules less than 10^6 daltons, which is still larger than most structural genes. **Perhaps the use of complementary nucleic acid fixed to an insoluble support will permit the fractionation of higher molecular weight ssDNA.** * * * **Using ssDNA isolation methods, it should be possible to determine linkage for the genes that code for the constant and variable parts of immunoglobulin molecules.**

Finally, one could isolate genes as single-stranded fragments and then replicate the complementary strand with a DNA polymerase, producing a duplex molecule suitable for gene control studies.

In the Protest, Gen-Probe relies on the first part of the second quoted paragraph and conveniently ignores the latter half. However, the latter half of the paragraph actually teaches away from the conclusion that Gen-Probe draws from the paragraph. Specifically, the authors note that the isolated genes might be increased in amount by a yet-to-be-discovered DNA

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polymerase or by *in vivo* cloning. More significantly, the authors then suggest a preference for cloning when one is dealing with an "impure mixture of DNA." Accordingly, when faced with an impure mixture of DNA, the authors direct one toward cloning, rather than amplification by DNA polymerase.

In an event, when viewed in context, the thrust of Brown's conclusion is that structural genes, once isolated by the methods described, are important for further and valuable studies but that other means may have to be developed to produce sufficient amounts of such genes. Thus, while the second paragraph speculates about combining purification and amplification to increase the amount of structural genes that one could produce, the theoretical methods "proposed" for purification and amplification were not available in that time period. At most, they present an invitation to experiment.

In particular, the paragraph first suggests purifying the gene about a thousand fold, but the highest level of purity discussed in the article is about fifty-fold (page 674). Gen-Probe's Protest quotes the "Large amounts of sequence-specific DNA" purified from mixtures of phage and bacterial DNAs, *see* page 7, but the papers on which that quote relies similarly do not reach anywhere near a thousand-fold increase in purity. Both references[27] teach immobilization of a complementary sequence to an affinity column followed by circulation of a sample containing the target sequence. Both references teach that the maximal purification of the target sequence is

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[27] Anthony J. Maziatis and Ekkehard K. F. Bautz, *Partial Isolation of an RIIB Segment of T_4 DNA by Hybridization with Homologous RNA*, Proc. Nat. Acad. Sci. USA, 57:1633-1637 (1967) (Ex. 12) and W. Stuart Riggsby, *A General Method for Fractionation of Nucleic Acids on the Basis of Sequence Homology*, Biochemistry 8:222-30 (1969) (Ex. 13).

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50-fold -- far less than the "thousand-fold" purification mentioned in Brown's concluding remarks.

Brown's wish for amplification at "hundreds to thousandsfold" is even farther removed from reality. No polymerase was known at the time that could satisfy that goal. H. Gobind Khorana and his group, who had been actively working towards amplifying large amounts of DNA, were never able to achieve meaningful levels of amplification. In their 1974 article[28], they wrote:

> None of the presently known DNA polymerases evidently utilizes a linear DNA duplex with even ends as a template or brings about the *de novo* synthesis of new polynucleotide chains. So far, it has only been possible to bring about "repair replication" by using single-stranded deoxypolynucleotides as templates and short polynucleotides complementary to one end of the template strands as primers. **Even so, in this primer-dependent replication, the reaction comes to a halt when the duplex has been completed and further synthesis requires separation of the duplex and a restart in the presence of an excess of the primer. Similarly, the problem of the extensive and orderly transcription of a defined deoxyribopolynucleotide remains to be solved.**

Id. at page 5213, emphasis added.

According to Dr. Mullis, the inventor of PCR, despite the significance of the work done in the Khorana laboratory in an effort to address this problem, that laboratory could not achieve significant levels of amplification:

> By 1974 the Khorana lab had done at least a few experiments with two primers and a synthetic duplex in the same tube. They had not discovered something shocking and had not published any detailed results of these experiments. They had made synthetic dsDNAs by diester

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[28] Amos Panet and H. Gobind Khorana, *Studies on Polynucleotides, The Linkage of Deoxyribopolynucleotide Templates to Cellulose and Replication*, J. Biol. Chem., 249:5213-5221 (1974) (Ex. 14).

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> synthesis and ligation of short ssDNAs, a method that, with the addition of very important improvements to the organic synthesis methodology, would still be in use in the 1980s. **Over a hundred papers chronicle the fact that many significant advances in nucleic acid chemistry were achieved during that era in that lab, but the use of DNA polymerase to make large quantities of DNA available from the tiny amounts in nature or created by organic synthesis was not one of them.**

Kary B. Mullis, *PCR and Scientific Invention: The Trial of DuPont vs. Cetus*, in THE POLYMERASE CHAIN REACTION, (Kary B. Mullis et al. eds., Birkhauser Boston, 1994) at page 437, emphasis added (Ex. 15).

The rationale for not pursuing polymerase-based amplification may be reflected in the concluding paragraph in Brown on which Gen-Probe relies. As noted above, the authors favored *"in vivo"* cloning in transformed bacteria where the gene of interest was in an impure mixture of DNA. *In vivo* cloning was apparently sufficiently successful that there was no incentive to continue efforts with *in vitro* polymerase-based amplification. In this regard, in the book MAKING PCR, author Paul Rabinow discusses the possibilities of amplification in the 1970's and, more particularly, the failure of polymerase-based amplification in comparison to *in vivo* cloning, stating:

> There was no inherent reason why the concept couldn't have been thought of during the 1970s, which leads us to speculate briefly on what factors might have been present to focus molecular biologists' and biochemists' attention elsewhere. One explanation is that techniques to manipulate DNA were still hierarchically dominated by concepts and systems in molecular biology and biochemistry. **Khorana and his colleagues were constructing a gene; they wanted multiple copies of it. Cloning, which emerged in the early 1970s, provided the means to achieve that end** - by harnessing known biological processes - yielding, if not *in vitro* exponential amplification, a sufficient number of *in vivo* amplified copies for the purposes at hand. *** * * Once techniques adequate to the task at hand became available to Khorana and his co-workers, they stopped exploring other possible means of amplifying DNA.**

Paul Rabinow, MAKING PCR, A STORY OF BIOTECHNOLOGY (Univ. Chicago Press 1996) at page 9, emphasis added (Ex. 16). Indeed, the globin gene that is cited repeatedly by Brown in the 1974 review to illustrate the type of gene that would benefit from the theoretical methods of purification and amplification was subsequently purified and amplified by cloning, rather than by *in vitro* amplification using a DNA polymerase.[29]

Accordingly, far from the "clear direction" urged by Gen-Probe, the concluding statements in the 1974 Brown review on purification and amplification were simple speculation. The true assessment of the value of such speculation lies in what lessons those in the art drew from it. As the court observed in *In re Oelrich,* 579 F.2d 86, 91, 198 U.S.P.Q. 210, 214 (C.C.P.A. 1978):

> In determining how the [prior art reference] was interpreted by those skilled in the art, we are more impressed by what those so skilled *did* than by what they *said.* Even though the words of the [prior art reference] implied that sub-critical operation was feasible, it was never, in fact, considered when a concrete problem requiring such operation was actually presented to two persons of ordinary skill in the art, both intimately familiar with the [prior art reference]. The actions by those skilled in the art reflected by this record indicate that the speculative statements of the [prior art reference] were recognized as such and ignored by those working in the art.

Emphasis in the original.

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29 *See* S. M. Tilgham et al., *Cloning Specific Segments of the Mammalian Genome: Bacteriophage Containing Mouse Globin and Surrounding Gene Sequences*, Proc. Natl. Acad. Sci. USA, 74:4406-4410 (1977) (Ex. 17); Stuart H. Orkin et al., *Cloning and Direct Examination of a Structurally Abnormal Human β °-thalassemia Globin Gene*, Proc. Natl. Acad. Sci. USA, 77:3558 3562 (1980) (Ex. 18); Elizabeth Lacy et al., *Isolation and Characterization of Mammalian Globin Genes*, in CELLULAR AND MOLECULAR REGULATION OF HEMOGLOBIN SWITCHING (Grune & Stratton 1979) (Ex. 19); A. P. Ryskov et al., *Purification of Large Native DNA Fragments Enriched in Globin Gene Sequences*, Gene, 3:81-85 (1978) (Ex. 20).

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Here, there is no evidence of any interest in the combination of purification and amplification for a period of 13 years, from the 1974 publication of the Brown paper to the filing of the application that led to the '338 patent. Indeed, those in the field, even esteemed laboratories with great interest in amplification by polymerase, such as Dr. Khorana's laboratory, were not able to achieve the proposed levels of amplification, let alone combine target capture and amplification. Thus, to paraphrase *Oelrich*, the actions of those in the art suggest that Brown's speculative statements "were recognized as such and ignored by those working in the art."

Even giving them the greatest possible weight, the speculative statements in Brown were merely a general invitation to experiment. Plainly such an invitation in 1974 cannot render obvious a specific method developed many years later. As the Federal Circuit noted in In *re Deuel,* 51 F.3d 1552, 1559, 34 U.S.P.Q.2d 1210, 1216 (Fed. Cir. 1995), "[a] general incentive does not make obvious a particular result, nor does the existence of the techniques by which those efforts can be carried out." Indeed, as the Federal Circuit observed in an analogous context in *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997), "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Moreover, even if it could be said that the speculative statements provided any motivation, the statements simply cannot have provided the required expectation of success. *See In re Vaeck,* 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991) (both a suggestion and a reasonable expectation of success are required for obviousness). As noted above, the cited levels of enrichment after purification and amplification were not obtainable at that time. In

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addition, where the DNA was part of an impure mixture, the type of mixture that one most typically faces, Brown's Conclusion actually taught away from the claimed combination by its express preference for amplification via *in vivo* cloning. Accordingly, contrary to Gen-Probe's arguments, the speculative statements in the 1974 Brown review did not suggest to anyone in the art that target capture should precede amplification in methods to detect polynucleotides.

In addition, when *in vitro* amplification techniques did become available with the discovery of PCR in 1985, there was created yet another powerful disincentive to employ target capture prior to such amplification processes. As noted extensively above and below, PCR was viewed as so specific that it was believed to be unnecessary to purify the target polynucleotide prior to amplification.

It was not until much later that those working in the field of developing nucleic acid detection assays fully appreciated the need for and desirability of the combination of target capture before *in vitro* amplification. Perhaps the most compelling evidence of this is apparent in Gen-Probe's own much later developed appreciation of the combination, discussed in detail above. At "www.Gen-probe.com" (Ex. 26), Gen-Probe offers a direct link to its self-described "Core Technologies." The second of its five "Core Technologies" is "Target Capture." The website identifies some of the advantages of this "new" technique of target capture as follows:

> Target Capture also:
> —Simplifies sample processing by eliminating centrifugation and chemical extraction steps.
> —Allows the simultaneous targeting of multiple nucleic acid sequences
> —Allows the use of large sample volumes.

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—Allows the use of a wide variety of samples such as cerebral spinal fluid and serum that are currently difficult to amplify.

—Increases specificity because the nucleic acid targets are purified before amplification.

The significance of target capture is also highlighted in a recent publication by Gen-Probe's Manager for Scientific Affairs. In a recent issue of IVD Technologys, Craig Hill writes:

> However, sample processing is typically the most troublesome part of these tests. It has been called the Achilles' heel of first-generation nucleic acid amplification tests.

See Craig Hill, *Automating Nucleic Acid Amplification Tests*, IVD Technology 6(7):36-45, 37 (Nov./Dec. 2000) (Ex. 21).

According to Hill, Gen-Probe's automated system employs a target capture process based on a pair of capture probes. The process is touted to "effectively remove inhibitors and interfering substances," thereby reducing false negatives. It is also said to simplify sample processing and makes automation easier. *Id.* at p. 38, column 3.

Despite the high value it now attributes to target capture prior to amplification, it appears that Gen-Probe came very late to this recognition. In fact, a review of Gen-Probe patents suggests that, despite the express mention of both techniques in several early patents,[30] Gen-Probe apparently did not appreciate the value of target capture prior to amplification until the 1996-97 time frame. Specifically, Gen-Probe's U.S. Patent No. 6,130,038, first filed in July of

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30 *See* Gen-Probe's U.S. Patent Nos. 5,399,491 (col. 2, lines 31-33) (Ex. 2); 5,639,599 (col. 2, lines 54-65) (Ex. 3); 5,731,148 (col. 14, lines 14-18) (Ex. 4); and 6,025,133 (col. 17, lines 19-22) (Ex. 5).

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1996, embodies the first mention of target capture prior to amplification. *See* '038 patent, col. 18, line 59 to col. 19, line 12 (Ex. 7).[31] Subsequently, the Gen-Probe patent that was filed in May 1997, U.S. Patent No. 6,110,678 (Ex. 6), expressly described a form of target capture prior to amplification as its invention at column 3, lines 38-63.

The timing of Gen-Probe's embrace of this combination does not appear to have been a coincidence. As the PTO is well aware, there is a pending lawsuit between Gen-Probe and the Patent Owner regarding the patent in reissue. As part of an effort to compel the production of documents relating to Gen-Probe's research and development activities in this area, the Patent Owner submitted the declaration of Dr. David J. Lane, a Senior Director in Research and Development, portions of which are relevant here. A copy of that declaration is submitted herewith (Ex. 27). Dr. Lane first noted that Gen-Probe's early automated assay systems did not use target capture (¶ 6) but that target capture became a noticeable addition in Gen-Probe publications relating to its assay systems in the spring of 1998 (¶ 9). In the interim, Gen-Probe hired some of Dr. Lane's former colleagues from Gene-Trak, where they focused on nucleic acid-based diagnostic assays for infectious diseases. These colleagues had worked extensively at Gene-Trak on the development of an automated assay using target capture and amplification (¶ 8). Accordingly, Gen-Probe's own actions demonstrate that the Brown 1974 article had not

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[31] That patent also identifies the benefits of the combination:

> A heterogeneous target capture method such as this is particularly advantageous since crude clinical samples can contain substances that inhibit or interfere with the amplification reaction. Thus, the ability to separate the target from such interfering substances can permit or enhance the sensitivity of nucleic acid amplification.

Col. 18, lines 50-55.

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suggested to Gen-Probe the answer to a difficult problem (the Achilles' heel of their assay methods) and the benefits of target capture prior to amplification. Rather, Gen-Probe's epiphany in this regard appears to have come after it gained access to information regarding the benefits of the technology embodied in the '338 patent.

C. Neither Arsenyan et al. Nor Syvanen et al. Provide Motivation to Combine Target Capture and Amplification

Arsenyan et al., a 1980 report on the isolation of rat liver 5S genes, cannot provide motivation to combine the target capture and amplification steps of the '338 patent in reissue because it embodies the teaching away set forth in the concluding remarks of the Brown 1974 review. As noted above, in the same paragraph on which Gen-Probe relies for motivation, the authors expressly favor *in vivo* cloning in transformed bacteria in cases where the gene of interest is in an impure mixture of DNA. Arsenyan isolated the gene of interest with two steps: "(a) enrichment of DNA fragments carrying the genes of interest, and (b) subsequent cloning and amplification of these fragments." The amplification was via cloning into the EcoRI site of pBR325, using E. coli as a host.[28]

Gen-Probe argues that Arsenyan provided motivation "to combine target capture with any form of amplification, including *in vitro* amplification." *See* Protest, page 9. However, Arsenyan does precisely the opposite. The authors actually discourage further *in vitro* work with the DNA that they purified. Instead, they promote cloning, i.e., "recombinant DNA technology," as the preferred route. They state:

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28 For the reasons set forth above, there is no question that the '338 patent in reissue was addressed to *in vitro* amplification.

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> The DNA fragments from rat liver, enriched in 5S rDNA, have been isolated by biochemical means. We believe that the purification procedure described above may be utilized for the purification of other individual genes as well. Unfortunately, the 5S DNA preparation is not pure enough for *in vitro* studies. The recombinant DNA technology offers another possibility for the isolation of genes in pure and intact form to study their structure and function directly.

See page 106, (c) Cloning of 5S DNA. Thus, Arsenyan cannot provide motivation for the claimed combination of target capture and amplification, let alone any reasonable likelihood of success.

Syvanen is even farther from the mark. It introduces a new and purportedly faster sandwich hybridization assay[29] and notes amplification as one method to possibly increase the sensitivity of the assay. The publication states "Consequently, the sensitivity of the method can be increased only by using probes of higher specific activity or by amplifying the target DNA." Page 5044. However, the article does not indicate that amplification should <u>follow</u> hybridization. The suggested purpose, to increase sensitivity, suggests <u>prior</u> amplification. At that time, the conventional method to increase the sensitivity of a hybridization assay by amplification was to amplify first to increase the amount of target that could then be detected by hybridization. *See* Gen-Probe U.S. Patent No. 5,399,491 (Ex. 2) (describing selective amplification as a way of increasing the sensitivity of assays at col. 2, lines 31-33).

Moreover, Syvanen actually teaches away from the benefit of the claimed combination, purifying the target polynucleotide prior to amplification, by suggesting that

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29 This paper was actually cited in the specification of the '338 patent for its disclosure of a two probe system for target capture. *See* col. 4, lines 46-51.

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purification is not necessary. For example, the Abstract states that "The test is insensitive to impurities in biological samples, which are analyzed without purification of the target DNA." Page 5037.

Accordingly, Syvanen does not provide motivation for the claimed combination of target capture and amplification.

D. The Prior Arguments for Nonobviousness Made During Prosecution of the '338 Patent Remain Sound and Are Supported by Gen-Probe's Own Documents

Gen-Probe contends that the prior arguments made by the Patent Owner during the prosecution of the '338 patent cannot overcome an obviousness rejection. It does so by mischaracterizing the prosecution history. Specifically, Gen-Probe urges that "applicants sought to focus discussion on PCR amplification, asserting that their invention solved previously unrecognized problems with PCR and represented an improvement of the PCR process," *(see* Protest, p. 15) but Gen-Probe complains that the effort was inappropriate because "clearly the claims are not *limited* to PCR or to any other form of target-specific amplification" *(id.* at 17, first paragraph).

In fact, as the foregoing summary of the original prosecution history demonstrates (§ I.B., above), it was the PTO that first raised the issue of PCR. In the prosecution of the '338 patent, the Patent Owner submitted a preliminary amendment in response to the restriction requirement and, to facilitate prosecution, introduced the Office Action that had been issued in U.S. Serial No. 07/944,505. That Office Action rejected all pending claims as unpatentable over Mullis, which disclosed "DNA amplification" and, as noted above, is the very famous PCR patent. To address that specific rejection, the Patent

Owner discussed, appropriately, the subject matter disclosed in Mullis. The Patent Owner noted, however, that:

> Nucleic acid targets can be amplified using any of a variety of methods. These **include** the polymerase chain reaction, PCR.

Preliminary Amendment of December 5, 1995, at page 12, emphasis added. *See* also note 8, *supra*.

The only other art-based rejection (Vary and Henson) similarly focused on PCR. *See* Office Action of June 26, 1996 and January 1, 1997, at pages 5 and 4 respectively.

Accordingly, the Patent Owner's arguments regarding PCR were simply responsive to the issues raised by the examiner. The fact of the matter is that the advantages manifested by the present invention in the context of PCR amplification are also manifested with the use of other *in vitro* enzymatic amplification techniques that produce a multitude of polynucleotide amplification products, such as that now employed by Gen-Probe.

Gen-Probe also attacks the specifics of the arguments raised during the prosecution, particularly the arguments embodied in the declaration of Dr. David Persing. For example, Gen-Probe quoted from Dr. Persing's paragraph 6, regarding the initial belief of practitioners that the targets did not have to be purified before amplification.[28] *See*

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[28] Gen-Probe also quotes Dr. Mullis as suggesting the need for purification by quoting his statement that "you do get a lot of other things replicating that you don't want." *See* Protest at page 18, footnote 6. However, Gen-Probe quoted selectively from that statement. His full statement reads "You do get a lot of other things replicating you don't want, but the background is low enough to be readable."

In that footnote, Gen-Probe also cites an editorial by Dr. Stuart Orkin on the benefits of (continued...)

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Protest at page 17-18. However, the literature supports Dr. Persing's statement. For example, in PCR TECHNOLOGY, the introductory chapter states:

> An important property of PCR, particularly in diagnostic applications, is the capacity to amplify a target sequence from crude DNA preparations as well as from degraded DNA templates.

PCR TECHNOLOGY (Henry A. Erlich ed., Stockton Press 1989) at page 4 (Ex. 22).

Similarly, the second chapter in PCR PROTOCOLS provides:

> One of the most appealing features of PCR is that the quantity and quality of the DNA sample to be subjected to amplification do not need to be high. A single cell or crude lysates prepared by simply boiling cells in water, or specimens with an average molecular length of only a few hundred base pairs, are usually adequate for successful amplification.

PCR PROTOCOLS, A GUIDE TO METHODS AND APPLICATIONS (Michael A. Innis et al. eds., Academic Press 1990) at page 14 (Ex. 23).

In contrast to those early beliefs, practitioners, including Craig Hill of Gen-Probe, now recognize that "sample processing" is the "most troublesome" part of nucleic acid tests, being the "Achilles' heel of first generation amplification tests." *See* Craig Hill, *Automating Nucleic Acid Amplification Tests*, at 37 (Ex. 21). And Gen-Probe's website

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[28](...continued)
the use of an elevated temperature in PCR to improve amplification over background. That notion actually teaches away from the present invention. The Orkin paper actually fully supports Dr. Persing's statements on the value attributed to amplification without purification. Specifically, in describing significant advances, Dr. Orkin notes:

> Second, Kogan and coworkers describe how small samples of blood or chorionic villus can be used in the amplification procedure without previous purification of the cellular DNA. This improvement circumvents losses of DNA during purification, leads to more rapid results, and should be compatible with automated amplification of DNA samples.

Orkin, page 1024, col. 2, paragraph 2.

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notes that "the major limitation of current nucleic acid amplification assays is the sample processing step which is usually complex, time-consuming, and often does not eliminate interfering substances that can inhibit the amplification reaction." Thus, Dr. Persing's statements are borne out by Gen-Probe's current and much publicized representations to the marketplace.

Gen-Probe also faults Dr. Persing's statements regarding the less-than-100% binding efficiency of a capture probe to its target, urging that "the only support offered for this conclusion is a statement from a 1993 publication." *See* Protest at page 19-20. However, Gen-Probe's own declarant, Dr. Michael M. Harpold, stated affirmatively that "target capture was known to be less than 100% efficient." *See* Declaration at page 10, line 4. Not surprisingly, the two experts draw different conclusions about motivation based on this level of efficiency, but Gen-Probe cannot attack Dr. Persing's statement when its own expert makes the same statement.

Finally, Gen-Probe criticizes Dr. Persing for relying on a generally unappreciated benefit -- that separation of the target prior to amplification removed potential amplification inhibitors -- urging that the art was well aware of the "beneficial effect of removing inhibiting substances." *See* Protest at pages 20-21. Yet, as noted above, Gen-Probe itself touts the removal of inhibiting substances as a primary advantage of Gen-Probe's "new" Target Capture process. *See* www.Gen-probe.com (Ex. 26) and Gen-Probe's '038 patent (col. 18, lines 50-55) (Ex. 7).

Accordingly, the arguments the Patent Owner made during the prosecution of the '338 patent were, and still are, valid arguments for nonobviousness.

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V. Newly Presented Claims 41-59 Find Complete Support in the Specification

Finally, Gen-Probe argues that each of the new claims 41-59 lack written description support because they are not limited to non-specific *in vitro* amplification, i.e., amplification based on non-specific primers. Gen-Probe's position is incorrect both as a matter of law and in light of the facts of this case.

Starting with the facts, the text of the '338 patent makes specific reference to the use of sequence specific primers at least twice. In example 5 at column 31 of the patent, the use of a non-specific "oligohexamer" primer is described. The example concludes, however, by teaching that "[a]lternatively, the double stranded DNA can be formed by synthesis starting from capture probe a." Capture probe a is a target specific oligonucleotide sequence. *See* col. 15, lines 39-51.

In addition, the discussion of the benefits of non-specific primers at column 30 of the '338 patent specifically mentions and necessarily implicates specific primers. The specification itself makes clear that the ability to use non-specific primers is an advantage of the system, not a necessary element of the invention, as follows:

> Amplification of the target nucleic acid sequence, because it follows purification of the target sequences, **can** employ non-specific enzymes or primers (i.e., enzymes or primers which are capable of causing the replication of virtually any nucleic acid). Although any background, non-target nucleic acids are replicated along with target, this is not a problem because most of the background nucleic acids have been removed in the course of the capture process. Thus no **specially tailored primers** are needed for each test, and the same standard amplification reagents can be used, regardless of the targets.

'338 Patent, col. 30, lines 30-40, emphasis added.

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The quoted paragraph makes specific reference to each of the two species of primers that can be used, i.e., "non-specific ... primers" and "specially tailored [e.g., specific] primers." The invention is disclosed generically with respect to "amplification" throughout the specification.

As to the law, even without express reference to the two species encompassed by the genus of primers useable in amplification (specific and nonspecific), disclosure of a genus embodying only two species describes each of these species. *In re Schaumann*, 572 F.2d 312, 197 U.S.P.G. 5 (C.C.P.A. 1978). Moreover, a generic disclosure, coupled with disclosure of one species, is a legally sufficient description of that genus minus the disclosed species. *In re Johnson,* 558 F.2d 1008, 1018, 194 U.S.P.Q. 187, 196 (C.C.P.A. 1977). Thus, the generic disclosure of "amplification" and the specific disclosure conceded by Gen-Probe of amplification with non-specific primers is a legally sufficient description of the only other species of the genus -- amplification with specific primers.

The Federal Circuit has made clear time and time again that "*ipsis verbis*" disclosure is not necessary to satisfy the written description requirement of section 112, first paragraph. *Fujikawa v. Wattenasin*, 93 F.3d 1559, 1570, 39 U.S.P.Q.2d 1895, 1904 (Fed. Cir. 1996). Instead, the disclosure "need only reasonably convey" to those in the art that the inventor had "possession" of the subject matter claimed. *Id.* More specifically,

> If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, **even if every nuance of the claims is not explicitly disclosed in the specification,** then the adequate written description requirement is met.

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In re Alton, 76 F.3d 1168, 1169, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996) (emphasis added). Thus, the written description requirement can be satisfied even if specific elements are not explicitly disclosed, so long as the specification as a whole conveys possession of an invention encompassing those specific elements.

Here, there is no question as to the breadth of disclosure conveyed by the specification. Specifically, the examiner concluded that the originally filed claims read on the Mullis PCR patent and rejected the claims for obviousness (not lack of written description) over that patent. The prototypical PCR reaction is one using specific primers. Thus, there can be no question that the specification conveys possession of an invention based on *in vitro* amplification using specific primers, such as those traditionally used in PCR.

Accordingly, the newly presented claims do fully comply with the written description requirement of Section 112, first paragraph.

VI. Conclusion

For the foregoing reasons, the originally filed claims and the newly presented claims are valid under Sections 102, 103, and 112, first paragraph. The Patent Owner respectfully suggests that the Protest lacks substantial merit and does not render the claims

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unpatentable under any of the theories advanced by Gen-Probe. Accordingly, the Patent Owner requests that the Office issue a statement to that effect.

If there are any fees due in connection with the filing of this Protest not already accounted for, please charge the fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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By: Jean Burke Fordis
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Dated: January 16, 2001

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